CASE REPORT

Erythema Nodosum Leprosum in a Treatment-Naïve Patient: Clinical Clues Not to Miss in Primary Care.

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Abstract
Leprosy is known as a "great mimicker" due to its broad spectrum of clinical presentations. Erythema nodosum leprosum (ENL), a Type 2 lepra reaction, typically manifests as acute, painful erythematous nodules during or after initiation of multidrug therapy (MDT) in multibacillary patients. We report a case of a 66-year-old treatment-naïve man who presented to primary care with chronic and painless nodules in the absence of classical lepromatous features or prior therapy. Slit-skin smear (SSS) confirmed multibacillary leprosy with a moderate bacterial index (BI) and an inactive morphological index (MI), supporting the diagnosis of chronic ENL. The patient responded well to a second-line MDT regimen and corticosteroids. This case highlights an unusual presentation of ENL preceding treatment and underscores the diagnostic challenges faced in primary care, particularly when classical signs of leprosy are absent. We discuss key differential diagnoses and the importance of early recognition to avoid misdiagnosis and prevent complications.

Keywords: *Clofazimine, erythema nodosum, multibacillary leprosy, Mycobacterium leprae.*

Introduction

Leprosy, or Hansen's disease, is a chronic granulomatous infection caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis,* primarily affecting the skin and peripheral nerves. The incubation period is notably long, ranging from 2 to 20 years, which can obscure early diagnosis and contribute to ongoing transmission [1]. Although the global burden has declined significantly with the widespread implementation of multidrug therapy (MDT), more than 200,000 new cases are still reported annually, particularly in endemic regions such as Southeast Asia, Africa, and South America [2]. Malaysia achieved the World Health Organization's (WHO) leprosy elimination target in 1994 (defined as <1 case per 10,000 population). However, sporadic cases continue to be reported, including in urban populations, partly due to migration and socioeconomic disparities [3]. This highlights the importance of clinical vigilance and awareness of atypical presentations among healthcare providers, particularly in primary care.

Leprosy is classified under the Ridley-Jopling system, with multibacillary forms—lepromatous and borderline lepromatous—carrying the highest bacillary load. A substantial number of these patients experience lepra reactions. Type 2 lepra reactions (ENL) are immune complex-mediated and commonly present with painful nodules, fever, neuritis, or arthritis. ENL occurs in multibacillary leprosy and approximately 50% of lepromatous leprosy patients and 5–10% of those with borderline lepromatous leprosy. ENL is typically observed during or after the commencement of MDT. Only a minority (2–10%) of patients develop ENL as the initial manifestation of leprosy [4]. These uncommon presentations, particularly in treatment-naïve individuals, pose diagnostic dilemmas in primary care settings. Recognizing these cases in the primary care setting is essential to avoid mismanagement, delayed treatment, and irreversible nerve damage.

Case report

A 66-year-old Malay man with underlying glucose-6-phosphate dehydrogenase (G6PD) deficiency and hypertension on amlodipine, presented with a one-year history of painless erythematous nodular lesions on the face, trunk, and upper limbs. The lesions began as periorbital oedema and nodules on the face, initially treated as an allergic reaction. He received both systemic and topical steroids, but the symptoms did not resolve. Over time, the lesions progressively spread and were associated with fatigue, bilateral lower limb oedema, and distal numbness of the hands and feet. He denied having fever, joint pain, or other systemic symptoms. Although he had resided in a leprosy-endemic area, he denied any known contact with leprosy patients, and all family members were reported to be healthy.

Examination revealed multiple symmetric erythematous to violaceous nodules and plaques on the face, trunk, and upper limbs, accompanied by bilateral lower limb pitting oedema (Figure 1). There was distal sensory loss without palpable nerve thickening. Slit skin smear (SSS) from the earlobes, elbows, and active lesions showed a bacterial index (BI) of 1.67 and a morphological index (MI) of 0.0, indicating moderate bacillary load with nonviable bacilli (Figure 2). These findings, together with the diffuse lesion distribution with systemic symptoms, are more suggestive of chronic ENL.

Laboratory investigations, including full blood count, renal and liver profiles, were normal, indicating no evidence of systemic organ involvement. Due to underlying G6PD deficiency, the patient was started on a second-line MDT regimen consisting of ofloxacin 400 mg daily, rifampicin 600 mg daily, clofazimine 50 mg daily and 300 mg monthly, along with pentoxifylline 400 mg three times per day and prednisolone 30 mg daily and tapering down. Regular follow-up was scheduled to monitor treatment response and manage potential side effects. After six months, repeat SSS showed a BI of 0.0. Lesions and lower limb oedema resolved completely (Figure 3).

Discussion

ENL typically presents with acute, tender erythematous papules, plaques, or nodules, often accompanied by systemic symptoms such as fever, malaise, or neuritis. Although pain is considered a hallmark of ENL [5], painless nodules may occur, particularly in chronic or recurrent ENL. Atypical presentations of ENL have also been reported, featuring a range of lesion morphologies, including pustular, vesiculobullous, ulcerative, necrotic, and erythema multiforme–like variants [6]. These uncommon forms can be easily overlooked in primary care settings, underscoring the importance of clinical vigilance and a high index of suspicion in endemic or high-risk populations. In many endemic regions, primary care is often the first point of contact for patients presenting with skin or neurological symptoms. Unfortunately, early signs of leprosy can resemble common benign dermatological or allergic conditions. In the absence of classical features such as hypopigmented or reddish skin lesions with sensory loss and nerve thickening, leprosy may be overlooked in the differential diagnosis. The delayed presentation in our patient highlights this diagnostic challenge and reinforces the importance of heightened clinical awareness and suspicion in primary care settings. In this case, the patient presented with generalised nodular lesions for a year before referral to dermatology, which were initially treated as allergic reactions without improvement. The chronicity and lack of response to therapy warranted an earlier skin biopsy to exclude other diagnoses. Although the slit-skin smear (SSS) ultimately confirmed lepromatous leprosy, the delay underscored the importance of early biopsy in persistent nodular dermatoses. Several differential diagnoses should be considered, including ENL, cutaneous sarcoidosis, lupus panniculitis, and erythema induratum [7]. ENL, in particular, can be easily misdiagnosed, resulting in delayed treatment that may lead to irreversible nerve damage, physical disability, and significant psychological distress. In primary care, thorough history-taking and examination are critical not only to suspect leprosy but also to systematically rule out other causes of chronic skin lesions.

Risk factors for leprosy include prolonged close contact with untreated individuals, residence in endemic regions, and genetic susceptibility, as certain host genes are known to influence immune response to *Mycobacterium leprae.* In this case, the patient had resided in a leprosy-endemic area for several decades but only developed clinical symptoms later in life. The long incubation period of leprosy is explained in this current presentation. This is due to the extremely slow replication rate of *Mycobacterium leprae* and its ability to persist within host macrophages and Schwann cells, evading immune surveillance for extended periods.

The clinical spectrum of leprosy is shaped by the host's immune response. Lepromatous leprosy is marked by a Th2-dominant humoral response, which fails to contain Mycobacterium leprae, resulting in a high bacillary load, minimal inflammation, and widespread skin lesions. In contrast, paucibacillary leprosy involves a Th1-driven cellular response, producing localised granulomatous inflammation. Erythema nodosum leprosum (ENL) is a Type III hypersensitivity reaction associated with multibacillary forms, triggered by immune complex deposition and characterised by neutrophilic vasculitis, which leads to painful erythematous nodules with systemic symptoms [11].

The slit-skin smear (SSS) examination played a pivotal role in confirming the diagnosis. While often underutilised in primary care due to a lack of expertise or facilities, SSS remains a cornerstone diagnostic tool for multibacillary leprosy. It allows direct visualisation of *Mycobacterium leprae* as acid-fast bacilli under microscopy, and provides both the bacterial index (BI) and morphological index (MI). These indices are critical for determining the bacillary load and viability, guiding treatment duration and prognostication. SSS has high specificity

(approaching 100%) for multibacillary leprosy but variable sensitivity (10–50%) depending on sampling site, technique, and disease stage [12]. Sampling multiple high-yield sites (such as earlobes and elbows) improves detection rates. While skin biopsy is the gold standard, providing histological confirmation through findings such as dermal granulomas, foamy histiocytes, and perineural involvement, it was not indicated in this case due to the clear clinical picture and positive bacteriological confirmation. Biopsy is indicated in smear-negative cases or when diagnostic uncertainty persists, especially in differentiating leprosy from other granulomatous or nodular dermatoses.

According to WHO guidelines, the standard MDT regimen for multibacillary leprosy includes rifampicin, dapsone, and clofazimine [1]. However, dapsone poses a significant risk of haemolysis in G6PD-deficient individuals. Our patient was G6PD-deficient and was therefore initiated on a second-line MDT regimen including ofloxacin, rifampicin, and clofazimine, along with pentoxifylline and tapering doses of prednisolone. Pentoxifylline, a phosphodiesterase inhibitor, has shown adjunctive benefit in ENL management due to its anti-inflammatory and vascular protective effects [13]. Corticosteroids effectively controlled the inflammatory manifestations of ENL in this patient. This case emphasises the need for individualised treatment regimens in patients with coexisting conditions. Screening for G6PD deficiency before initiating dapsone is essential to avoid life-threatening haemolysis.

Although Malaysia achieved the WHO's leprosy elimination target in 1994, sporadic cases are still reported [3]. Factors such as migration, urban overcrowding, and limited healthcare access continue to contribute to ongoing transmission. Early diagnosis remains essential to prevent irreversible nerve damage, deformities, and further spread. In this context, primary care practitioners play a crucial role as the first point of contact. Timely referral for dermatological and microbiological evaluation is essential to break the chain of delayed diagnosis and improve patient outcomes.

Conclusion

This case highlights the need for heightened clinical suspicion in primary care settings when encountering chronic, unexplained nodular skin lesions—particularly in patients with neuropathy or a history of exposure in endemic areas. The slit-skin smear, though often underutilised, is a simple and cost-effective diagnostic tool that can be employed even in primary care. By recognising presentations early, primary care practitioners can play a vital role in early detection, disability prevention, and supporting national leprosy elimination efforts.

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Conflicts of interest

All authors declare no conflicts of interest.

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Authors contribution

FH contributed to manuscript preparation, data collection, and revisions. SS contributed to the manuscript review, editing, and final approval.

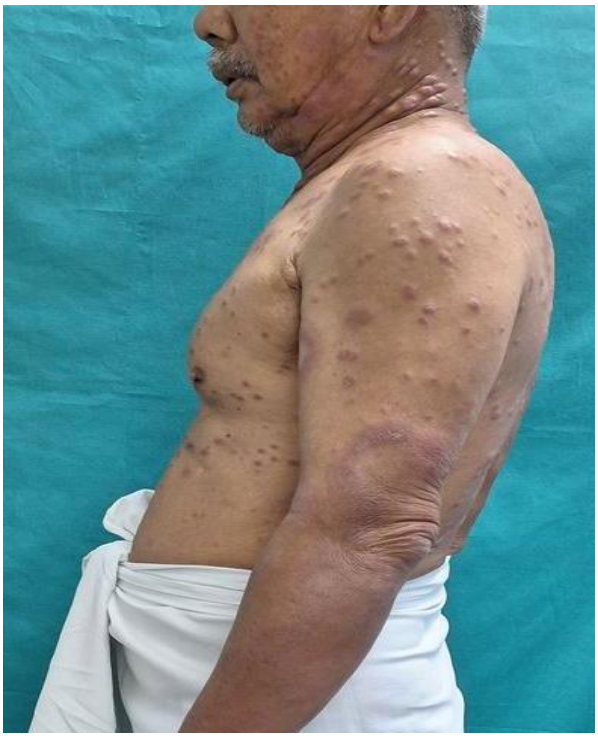

Figure 1. Multiple erythematous to violaceous nodules or plaques of varying sizes at upper part of body.

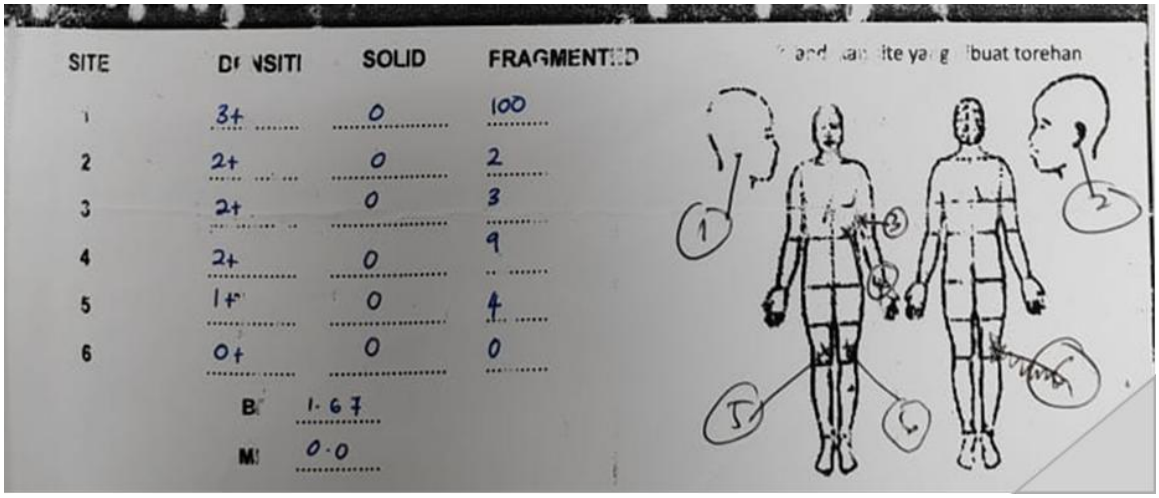

Figure 2. Slit skin smear results with bacterial and morphological indices across multiple body sites.

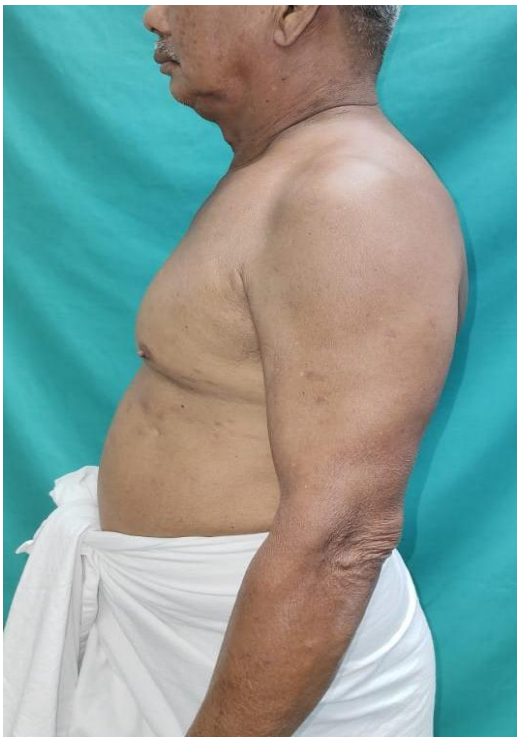

Figure 3. 6 months on treatment showed resolution of nodules.

Table 1. Features of Differential Diagnosis of Chronic Nodular Skin Lesions

Condition	Lesion Appearance	Associated Symptoms	Diagnostic Tests
ENL [4]	Tender erythematous subcutaneous nodules, typically on face and extremities	Fever, neuritis, arthralgia, oedema	Slit-skin smear (AFB), skin biopsy (neutrophilic infiltrate/vasculitis)
Cutaneous Sarcoidosis [8]	Firm, non-tender papules, nodules, or plaques; may be skin-coloured or violaceous	Cough, dyspnoea, lymphadenopathy, fatigue	Skin biopsy (non-caseating granulomas), chest radiograph, serum ACE
Erythema Induratum [9]	Nodules or lumps usually on posterior legs; red purple discolouration, may ulcerate	History of Tuberculosis contact	Skin biopsy (lobular panniculitis with vasculitis), TST/ IGRA,
Lupus Panniculitis [10]	Deep, firm subcutaneous nodules with overlying erythematous or atrophic skin	Photosensitivity, arthralgia, fatigue, systemic lupus erythematosus signs	ANA, anti-dsDNA, skin biopsy (hyaline fat necrosis)

Abbreviations:
AFB – Acid-Fast Bacilli; ANA – Antinuclear Antibody; anti-dsDNA – Anti–double-stranded DNA.
ACE – Angiotensin-Converting Enzyme; IGRA – Interferon Gamma Release Assay. TST – Tuberculin Skin Test

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